Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claims 1 and 8 have been amended, and new claim 31 has been introduced. The amendments to the preamble and "wherein" clause of claim 1 are supported at paragraphs [0003]–[0006] and [0013]–[0014], and the Examples. New claim 31 finds descriptive support in original claim 1 as well as in paragraphs [0034]-[0037]. Therefore, no new matter has been introduced by these claims. Claims 1-17 and 31 are pending. No excess claim fees are due with this submission.

The rejection of claims 1-17 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments and the following remarks.

As for claim 1, the position of the U.S. Patent and Trademark Office ("PTO") is that it is unclear what "in the absence of the other nucleotides of the target nucleic acid sequence" means. Applicants respectfully disagree.

It is clear from the present application that the objected language refers to a subset of the target nucleic acid molecule sequence—the specific identified hairpin sequence, alone, separate and apart from the remaining portions of the target nucleic acid molecule used during the first "predicting" step of claim 1. This is described at paragraph [0034] of the present application. This paragraph recites that, having identified hairpin structures within the folded structure of the prospective target nucleic acid molecule, the hairpin sequences are isolated from the larger sequence that was used as input to the folding software. The isolation can be performed *in silico*. Once isolated, the hairpin sequence, alone, is then subjected to the second "predicting" step.

From the description of the present invention, it is clear that the identified hairpin nucleotide sequence is necessarily shorter than the provided target nucleic acid sequence, and the second "predicting" step concerns only this shorter identified hairpin sequence rather than the entire target nucleic acid molecule used for the first "predicting" step. One of skill in the art, having read the description of the invention, would fully understand what is meant by this claim language.

The remaining amendments to claims 1 and 8 overcome the two other bases of rejection asserted on page 3 of the office action.

For all these reasons, the rejection of claims 1-17 for indefiniteness should be withdrawn.

The rejection of claims 1-3 under 35 U.S.C. § 102(b) for anticipation by Zuker et al., "Optimal Computer Folding of Large RNA Sequences Using Thermodynamics and Auxiliary Information," *Nucl Acids Res* 9(1):133-148 (1981) ("Zuker") is respectfully traversed.

Zuker discloses a computer method for folding an RNA molecule that finds a conformation of minimum free energy using published values of stacking and destabilizing energies. Its power is demonstrated in the folding of a 459 nucleotide immunoglobulin γ1 heavy chain messenger RNA fragment (Figure 3) and a fragment from the 16S ribosomal RNA of *Escherichia coli* (Figure 4).

While Zuker certainly predicts a folded structure of a nucleic acid molecule (in figures 3 and 4), it is not apparent that Zuker actually identifies a sequence of a hairpin within the folded structure (although their presence is shown). Zuker certainly fails to teach or suggest predicting a folded structure for a hairpin *per se* (separate and apart from the molecules shown in Figures 3 and 4). While molecules of Figure 3 and 4 contain shorter hairpin segments, no hairpin sequence is identified therein. The Gibbs free energy of the smaller hairpin sequence are not calculated independently. Thus, Zuker also fails to teach or suggest whether any of the hairpins within the larger structures of Figures 3 or 4, alone, has a predicted Gibbs free energy of at most about - 3 kcal/mol. Thus, Zuker fails to teach or suggest the "identifying" and second "predicting" steps recited in claim 1.

Given these deficiencies, the rejection of claims 1-3 for anticipation by Zuker is improper and should be withdrawn.

Applicants further submit that new claim 31 is patentable over Zuker. As noted above with respect to claim 1, Zuker does not actually identify a sequence of a hairpin within the folded structure (although their presence is shown). Moreover, because Zuker fails to teach or suggest predicting a folded structure for a hairpin *per se* and does not calculate independently the Gibbs free energy of the smaller hairpin sequence or its binding to a target nucleic acid molecule, Zuker fails to teach or suggest determining whether (i) self-folding of the identified hairpin and (ii) hairpin binding over its entire length to the target nucleic acid molecule will be energetically

favorable. Thus, Zuker fails to teach or suggest the "identifying" and "determining" steps as recited in claim 31.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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